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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/305,390	05/05/99	YAMAMOTO	H	06501/030001

HM22/0315

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EXAMINER	
HUTSON,R	
ART UNIT	**PAPER NUMBER**
1652	12

DATE MAILED: 03/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/305,390	Yamamoto
Examiner	**Group Art Unit**
Richard Hutson	1652

☒ Responsive to communication(s) filed on Jan 5, 2000

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-22 is/are pending in the applicat

Of the above, claim(s) 1-6, 11, 13, and 15-18 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 7-10, 12, 14, and 19-22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7 & 11

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election without traverse of group II, claims 7-14 and 19-22 in Paper No. 10 is acknowledged. It is noted that the examiner mistakenly grouped claims 11 and 13 with group II, when they should be grouped with group I, claims 1-6 and 15-18 restriction.

Claims 1-6, 11, 13 and 15-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The requirement is deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 7-10, 12, 14 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with acetoacetyl-CoA reductase having the amino acid sequence shown in SEQ ID NO: 9, does not reasonably provide enablement for a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with **any**

protein capable of reducing 4-halo-acetoacetic acid ester or its derivative to produce (S)-4-halo-3-hydroxybutyric acid ester. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 7-10, 12, 14 and 19-22 are so broad as to encompass a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with any protein capable of reducing 4-halo-acetoacetic acid ester or its derivative to produce (S)-4-halo-3-hydroxybutyric acid ester. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of acetoacetyl-CoA reductase enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the acetoacetyl-CoA reductase having the amino acid sequence shown in SEQ ID NO: 9.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a

reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any acetoacetyl-CoA reductase because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting 4-halo-acetoacetic acid ester reductase activity; (B) the general tolerance of acetoacetyl-CoA reductase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any acetoacetyl-CoA reductase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of proteins having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

3. Claims 7-10 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7-10, 12, 14 and 19-22 are directed to all possible methods for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with **all possible** proteins capable of reducing 4-halo-acetoacetic acid ester or its derivative to produce (S)-4-halo-3-hydroxybutyric acid ester. The specification, however, only provides a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with a single representative species of acetoacetyl-CoA reductase, i.e. that corresponding to SEQ ID NO: 9, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of this protein by any identifying structural characteristics or properties other than the activities recited in the claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 10 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite in the recitation of "hybridizable" as this term is unclear absent a statement of the conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> >
> > (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 7, 10, 12 and 19 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Matsuyama et al. (U.S. Patent No.: 5,559,030).

Matsuyama et al. (U.S. Patent No.: 5,559,030) teach a process for the production of optically active 4-halo-3-hydroxybutyric acid ester characterized by permitting a microorganism or a preparation thereof to act on a 4-halo-3-acetoacetic acid ester and harvesting the product the optically active 4-halo-3-hydroxybutyric acid ester. Specifically the halogen atom in the 4-haloacetoacetic acid ester taught is chlorine, bromine, iodine or so on. Matsuyama et al. further teach that certain microorganisms produce a (S)-4-halo-3-hydroxybutyric acid ester and others produce a (R)-4-halo-3-hydroxybutyric acid ester. Since it is known that the catalyst of the actual chemical reaction is an enzyme found within the said microorganism or preparation thereof, Matsuyama et al. anticipates a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with acetoacetyl-CoA reductase constituting the poly-β-hydroxy fatty acid biosynthesis system. It is believed that acetoacetyl-CoA reductase is the enzyme within said microorganisms that is responsible for the enzymatic reduction reaction above, regardless, claim 10 (b) reads on any enzyme capable of catalyzing this reaction. Further it would have been obvious to one of ordinary skill in the art at the time of filing to purify from said microorganism the enzyme which catalyzes the reduction of 4-halo-acetoacetic acid ester to (S)-4-halo-3-hydroxybutyric acid ester so that the method of production could be performed *in vitro* or recombinantly.

8. Claim 7 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Kimoto et al. (U.S. Patent No.: 6,001,618).

Kimoto et al. (U.S. Patent No.: 6,001,618) teach an enzyme, isolated from the microorganism belonging to the genus *Kluyveromyces*, for use in a method for producing (S)-4-halo-3-hydroxybutyric acid esters. Therefore, Kimoto et al. anticipates claims 7 and 10.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 8, 9, 14, 20, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al. (U.S. Patent No.: 5,559,030) in view of Peoples et al. (U.S. Patent No.: 5,229,279) or Summerville et al. (WO 93/02187).

As discussed above, Matsuyama et al. teach a process for the production of optically active (S)-4-halo-3-hydroxybutyric acid ester. Matsuyama et al. do not teach the production of optically active 4-halo-3-hydroxybutyric acid ester using an acetoacetyl-CoA reductase derived from a microorganism derived from the genus *Ralstonia*, or specifically *Ralstonia eutropha*.

Peoples et al. (U.S. Patent No.: 5,229,279) teach a method for constructing a polyhydroxybutyrate-like polyester polymers in a bacterial host by providing the isolated structural genes encoding beta-ketothiolase, acetoacetyl-CoA reductase and polyhydroxybutyrate

polymerase. Specifically, Peoples et al. identified and cloned the acetoacetyl-CoA reductase gene from *A. eutrophus* (the former name of *Ralstonia eutropha*) and express this gene in *E. coli.*

Somerville et al. (WO 93/02187) teach a transgenic plant and a method for the production of poly-beta-D-hydroxybutyric acids and related polyhydroxyalkanoates by the introduction of the DNA which encodes the enzymes responsible for the production of polyhydroxybutyrate into cells of higher plants. Somerville et al. specifically teach the use of an isolated DNA which encodes the PHB operon from *A. eutrophus*. including the enzyme acetoacetyl-CoA reductase which converts acetoacetyl-CoA to D(-)-3-hydroxybutryryl-CoA. In plants and animals acetoacetyl-CoA is a precursor in the production of mevalonate. Alignment of the nucleotide sequence of acetoacetyl-CoA reductase of Somerville et al., SEQ ID NO: 1 with the nucleotide sequence encoding acetoacetyl-CoA of instant application, SEQ ID NO: 10, shows that they are 100 % identical. Somerville et al. also teach that A. eutrophus appears to have two isoenzymes of acetoacetyl-CoA reductase which differ with respect to substrate specificities and cofactor requirements. The NADH reductase is active with C4 to C10 D(-)- and L(+)-3-hydroxyacyl-CoAs, whereas the NADPH reductase is active with only C4 and C5 D(-)-3-hydroxyacyl-CoAs.

One of ordinary skill at the time of filing would have been motivated to design a method for method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative as taught by Matsuyama et al. using the acetoacetyl-CoA reductase constituting the poly-β-hydroxy fatty acid biosynthesis system from Alcaligenes eutrophus (Ralstonia eutropha) as taught by Peoples et al. or Summerville et al. The

motivation in using the acetoacetyl-CoA reductases of Peoples et al. or Summerville et al. is that the nucleic acids encoding these enzyme have been cloned and therefore this allows for more control in the reaction conditions and the opportunity to improve the enzyme by the use of recombinant technologies and mutagenesis. Therefore, claims 8, 9, 14, 20, 21 and 22 are made obvious by Matsuyama et al,. Peoples et al. and Summerville et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson Ph.D.
3/10/2000

Rebecca Prouty

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